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Mitochondrial Dysfunction Indirectly Elevates ROS Production by the Endoplasmic Reticulum

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Mitochondrial dysfunction is often associated with increased reactive oxygen species (ROS) production by the organelle itself. Leadsham et al. (2013) now show that the link between mitochondrial damage and ROS is more complicated, at least in yeast, where signals from damaged mitochondria increase ROS production from the endoplasmic reticulum surface.

The production of reactive oxygen species (ROS) by mitochondria was first recognized in the 1960s (Jensen, 1966; Murphy, 2009). Since then, it has become clear that, in metazoans at least, mitochondrial ROS production can occur by the production of superoxide from complexes I and III, although other sites also contribute (Murphy, 2009). This superoxide production leads to the formation of hydrogen peroxide, and together with other downstream products, these ROS cause nonspecific oxidative damage that contributes to a number of pathologies and has also been linked with aging in general (Harman, 1972; Wallace, 2010). There is growing evidence that mitochondrial ROS production is also involved in redox signaling (Finkel, 2011), for example in T cell activation (Sena et al., 2013). One tacit assumption in all these studies has been that changes in ROS levels associated with alterations in mitochondrial activity are caused by disruption to mitochondrial metabolism itself, for example by the accumulation of NADH in dysfunctional mitochondria (Murphy, 2009). In this issue of *Cell Metabolism*, Leadsham et al. show that the situation is more complicated and present compelling evidence that while mitochondrial dysfunction in yeast does increase ROS levels, this is primarily due to superoxide production from the surface of the endoplasmic reticulum (ER) and not from the mitochondria themselves (Leadsham et al., 2013).

When the yeast *Saccharomyces cerevisiae* has used up all available fermentable substrates, such as glucose, it switches to oxidative metabolism, a process known as the diauxic shift, which necessitates the activation of mitochondrial metabolism. Leadsham et al. (2013) found that when cytochrome oxidase, the terminal component of the mitochondrial respiratory chain, was inactivated during the diauxic shift, there was an increase in ROS that led to a decrease in cell viability (Figure 1). Surprisingly, further experiments such as preventing assembly of the respiratory chain by removing mitochondrial DNA showed that these ROS were not coming from the mitochondria. In tracking down the ROS source, the authors came across an unexpected signaling pathway linking mitochondrial dysfunction to an elevation of cytosolic ROS. The first step is the recruitment of the regulatory GTPase RAS from the cytosol to the surface of mitochondria. This localization requires *BDF1*, which encodes a bromodomain-containing TFIID binding protein, although how this protein acts to recruit RAS to mitochondria remains unclear. The authors next showed that the source of cytosolic superoxide and hydrogen peroxide was the NADPH oxidase Yno1p, which is found on the surface of the ER. RAS localization to the outer membrane of dysfunctional mitochondria somehow suppresses the activity of the endoplasmic reticulum-associated degradation (ERAD) pathway, an endogenous protein degradation pathway, which ubiquitinylates proteins for degradation as part of ER protein quality control. RAS-dependent suppression of ERAD stabilizes Yno1p to enable the production of large amounts of superoxide that leads to decreased cell viability.

As with all surprising results, this work raises more questions than it answers. Among these is how mitochondrial dysfunction is sensed. The mitochondrial damage was initially established by decreasing expression of cytochrome oxidase. However, the uncoupler FCCP, which abolishes the mitochondrial protonmotive force, also led to mitochondrial RAS accumulation, suggesting that disruption to the respiratory chain, by decreased expression of cytochrome oxidase, leads to defective proton pumping, which in turn lowers the protonmotive force. As many types of mitochondrial damage will lower the protonmotive force, this is a plausible strategy for sensing generalized mitochondrial dysfunction. Furthermore, it has parallels with the PINK1/Parkin system in mammals, in which mitochondria with low protonmotive force accumulate PINK1 on their surface, leading to recruitment of the ubiquitin ligase Parkin that initiates the selective removal of dysfunctional mitochondria by mitophagy (Narendra and Youle, 2011). Future work will explore these parallels in more detail and will hopefully shed light on the role of the transcription factor BDF1 in promoting the recruitment of RAS to the mitochondrial surface. It may be that the changes in ROS levels due to increased Ynop1 activity are important in shifting the cell to a state that can better deal with damaged mitochondria, or perhaps prevents cells with damaged mitochondria from dividing. In this regard, NADPH oxidases are involved in a number of redox signaling pathways (Finkel, 2011; Gough and Cotter, 2011); thus changes in ROS production from Yno1p are a plausible candidate for this role. However, suppression of ERAD may also be a consequence of diversion of the protein turnover machinery to degrade damaged mitochondria, with the unintended consequence of increased activity of Yno1p on the ER surface.

It is too early to say how closely this work in yeast relates to mammalian systems. There are many significant differences between yeast and mammals, notably the lack of complex I in *S. cerevisiae*, and major differences in the mechanisms of cell death. Even so, the link between a defect in cytochrome oxidase and an increase in ROS is intriguing, as decreased activity of this enzyme has been reported in a number of neurodegenerative diseases (Coskun et al., 2012). More generally, the link between cell protein degradation pathways and the turnover of damaged mitochondria is a potentially fertile area of investigation, especially as the mitochondrial RAS localization has parallels with the mechanisms disrupted in inherited forms of Parkinson's disease (Coskun et al., 2012; Narendra and Youle, 2011).

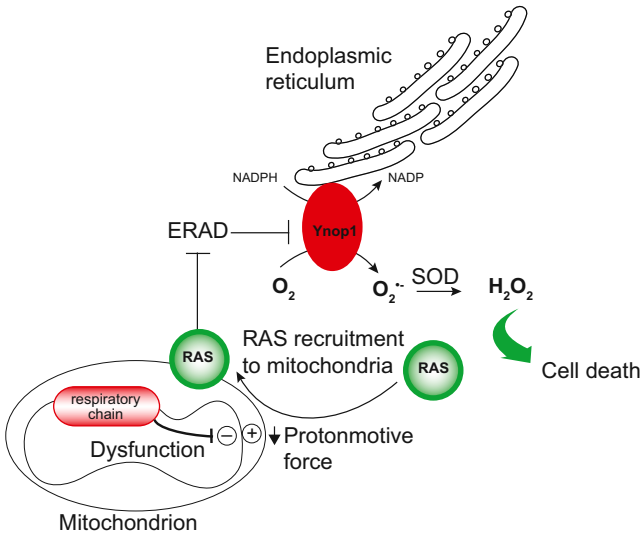

Figure 1. Activation of Endoplasmic Reticulum ROS Production in Response to Mitochondrial Dysfunction

In this model mitochondrial dysfunction affects the ability of the respiratory chain to sustain a protonmotive force across the mitochondrial inner membrane, indicated by the positive charge outside the mitochondrion and the negative charge inside. This leads to the accumulation of the GTPase RAS on the surface of the mitochondrial outer membrane, which in turn suppresses the endoplasmic reticulum-associated degradation (ERAD) pathway. As a consequence, the accumulation of the NADPH oxidase Ynop1 on the surface of the ER increases the production of superoxide, which is then dismutated to hydrogen peroxide by superoxide dismutase (SOD). Accumulation of ROS in response to mitochondrial dysfunction leads to cell death.

In conclusion, the work by Leadsham et al. greatly expands our view of how mitochondrial dysfunction interacts with the cell's redox environment. It is now clear that an alteration in cytosolic ROS can be generated indirectly from mitochondrial dysfunction, adding an interesting new dimension to how mitochondrial metabolism links to changes in ROS. In addition, the specific signaling pathways uncovered in this study linking mitochondrial dysfunction with protein turnover and NADPH oxidases suggest many new lines of investigation for exploring the roles of mitochondrial dysfunction in degenerative diseases.

REFERENCES

Coskun, P., Wyrembak, J., Schriner, S.E., Chen, H.W., Marciniack, C., Laferla, F., and Wallace, D.C. (2012). Biochim. Biophys. Acta *1820*, 553–564.

Finkel, T. (2011). J. Cell Biol. *194*, 7–15.

Gough, D.R., and Cotter, T.G. (2011). Cell Death Dis *2*, e213.

Harman, D. (1972). J. Am. Geriatr. Soc. *20*, 145–147.

Jensen, P.K. (1966). Biochim. Biophys. Acta *122*, 157–166.

Leadsham, J.E., Sanders, G., Giannaki, S., Bastow, E., Hutton, R., Naemi, W.R., Breitenbach, M., and Gourlay, C.W. (2013). Cell Metab. *18*, this issue, 279–286.

Murphy, M.P. (2009). Biochem. J. *417*, 1–13.

Narendra, D.P., and Youle, R.J. (2011). Antioxid. Redox Signal. *14*, 1929–1938.

Sena, L.A., Li, S., Jairaman, A., Prakriya, M., Ezponda, T., Hildeman, D.A., Wang, C.R., Schumacker, P.T., Licht, J.D., Perlman, H., et al. (2013). Immunity *38*, 225–236.

Wallace, D.C. (2010). Environ. Mol. Mutagen. *51*, 440–450.